REMARKS

Claims 21-32 are pending in the instant application. A complete list of the pending claims is presented above. Reconsideration of the claims in light of the following remarks is respectfully requested.

Claim Rejections

A. 35 U.S.C. § 112, First Paragraph

1. New Matter

Claims 21-32 stand rejected under 35 U.S.C. § 112, first paragraph., as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the Examiner asserts that the modified nucleotides comprising covalently attached electron transfer moieties (ETMs) and methods of making nucleic acids incorporating such modified nucleotides is not supported by any description in the specification as filed. As is discussed at length below, Applicants submit that the specification, read in view of the existing prior art, provides clear description of enzymatic incorporation of nucleotides labeled with bulky adducts into nucleic acids, and therefore the pending claims do not introduce new matter. Accordingly, withdrawal of this rejection is respectfully requested.

2. Lack of Written Description

Claims 21-32 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the

application was filed. In particular, the Examiner asserts that the specification fails to describe the claimed modified nucleotide comprising a covalently attached ETM (a "bulky adduct") or methods of making nucleic acids using such modified nucleotides. Applicants disagree with this assertion for the reasons outlined below.

The essential purpose of the written description requirement is to show the possession of the invention as of the filing date as a *prima facie* date of the invention. *In re Smith*, 481 F.2d 910, 178 U.S.P.Q. 620, 623 (CCPA 1973). Accordingly, the specification is required to contain a statement that adequately describes the invention as claimed. However, the invention need not be described in *ipsis verbis* in order to satisfy the description requirement. *In re Luckach, Olson and Spurlin*, 169 U.S.P.Q. 795, 796 (CCPA 1971). It is sufficient to satisfy the written description requirement if the

> specification contains a statement of the appellant's invention which is as broad as appellant's broadest claims....

In re Robbins, 420, F.2d 452, 166 U.S.P.Q. 552, 555 (CCPA 1970)

> It is only required, for example, that the specification describe the invention sufficiently for those of ordinary skill in the art to recognize that the applicant invented the subject matter he now claims.

In re Voss, 557 F.2d 812, 194 USPQ 267, 271 (CCPA 1977)

Applicants submit that the specification as filed provides a legally sufficient written description for modified nucleosides comprising covalently attached ETMs and the incorporation of such nucleosides into a growing nucleic acid. For example, page 23, lines 11-23 of the specification teaches:

> In a further embodiment for the modification of internal residues, 2' or 3' modified nucleoside triphosphates are generated using the techniques described above for the 3' nucleotide modification. The modified nucleosides are inserted internally into nucleic acid using standard molecular biological techniques for labelling DNA and RNA. Enzymes used for said labelling include DNA polymerases such as polymerase I, T4 DNA polymerase, T7 DNA polymerase, Taq DNA polymerase, reverse transcriptase and RNA polymerases such as E. coli RNA polymerase or the RNA polymerases from phages SP6, T7 or T3 (Short Protocols in Molecular Biology, 1992. Ausubel et al. Ed. pp 3.11-3.30).

In addition, in determining if sufficient written description for the claims exists in the specification as filed, it is respectfully pointed out that the Examiner must interpret that specification in light of the prior art. Accordingly, Applicants filed a chapter published in a commercially available Handbook by Molecular Probes to provide context for the instant application with the Response of February 13, 2002. "Chemically modified nucleotides, oligonucleotides and nucleic acids": Chapter 8 – Section 8.2 in the 'Handbook of Fluorescent Probes and Research Chemicals' by Richard P. Haugland, 6th edition. This exhibit is resubmitted, for the Examiner's convenience, as Exhibit A. It is noted that this submission, and all other submitted references with dates after the filing date of the instant application are provided not to supplement the disclosure of the application; rather, the subsequent work is present to show that the utility asserted and shown in the application is supported by further research, and that the specification fully describes claims. See In re Wilso, 135 USPQ 442, 444 (CCPA 1962); Ex parte Obukowicz, 27 USPQ 1063 (BPAI); Gould v. Quigg, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987):

> it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case the late dated publication was not offered as

> evidence for this purpose. Rather, it was offered . . . as evidence that the disclosed device would have been operative..."

In response to the Applicants' submission, the Examiner dismissed Exhibit A as irrelevant in that it does not specifically describe the attachment of electron transfer moieties to nucleotides. While the Exhibit does not specifically refer to electron transfer moieties, it does explicitly counter the assumption made by the Examiner regarding enzymatic or chemical addition of bulky adducts that forms the basis for this rejection. In particular, the Examiner has asserted that bulky adducts, such as electron transfer moieties or fluorophore labels, cannot be attached to nucleotides which are subsequently incorporated during nucleic acid synthesis. However, as stated by the Examiner on page 4 of the pending Office Action, Exhibit A describes the chemical and enzymatic addition of nucleotides labeled with bulky fluorophore labels into nucleic acids.

In addition, merely because the Examiner can point to a reference, Bannworth et al., which teaches an alternative method of electron transfer moiety attachment, it does not follow that other means are not possible, such as the instant invention. This is especially true as the reference is silent to such alternative methods. In fact, Applicants assert that a person of ordinary skill in the art would know that modified nucleosides with "bulky groups" such as transition metals and other "bulky" fluorescent molecules attached to the base could be incorporated during enzymatic or chemical synthesis of nucleic acids. Applicants present below several articles in support of this position, and clearly counter the Examiner's inference from the Bannworth et al reference.

Tesler, et al., for example, supports the Applicants' position as it teaches the incorporation of a bulky label compound to an internal base of a DNA octomer. Tesler, *et al.*, J. Am. Chem. Soc., 111:7226-7232 (1989) attached hereto as Exhibit B. Other examples include the construction of a 5'-dye-labeled nucleoside phosphoramidite reagent for use as primers in a modified Sanger protocol (US Patent No. 4,415,732, attached hereto as Exhibit C) and Sinha and Stripke's description of methods of synthesizing oligonucleotides with reporter groups, such as fluorphores, chromophores, biotin, etc., using solid phase phosphoramidite chemistry (Sinha and Stripke, "Oligonucleotides with reporter groups attached to the 5'-terminus", Oligonucleotides and Analogues, ed. F. Eckstein, Oxford University Press, Oxford, 195-210, 1991, attached hereto as Exhibit D). In addition, Conway *et al.*, describe the sequence-specific attachment of reporter molecules to the backbone of DNA using internal phosphodiesters. Conway *et al.*, "Site-specific attachment of labels to the DNA backbone", Oligonucleotides and Analogues, ed. F. Eckstein, Oxford University Press, Oxford, 195-210, 1991, attached hereto as Exhibit E. Similarly, Ruth teaches the labeling of oligonucleotides with reporter groups. Ruth, J. L., "Oligonucleotides with reporter groups attached to the base", Oligonucleotides and Analogues, ed. F. Eckstein, Oxford University Press, Oxford, 255-282, 1991, attached hereto as Exhibit F. Ruth also teaches the attachment of such bulky reporter groups via linkers at pages 268-270.

Furthermore, art cited in the instant application at page 21, lines 13-14, teaches that bulky groups at the 2' position of a nucleotide do not interfere with synthesis of nucleic acids incorporating such modified nucleotides. The Applicants direct the examiner to Exhibit G (Gait et al., "Oligoribonucleotide Synthesis" Oligonucleotides and Analogues, ed. F. Eckstein, Oxford University Press, Oxford, 25-48 1991). Gait et al. show that presence of a t-butyldimethylsilyl

group on the 2' position of a ribose nucleoside does not interfere with the coupling of the 3' phosphoramidite with the free 5' OH group of nucleotide of the growing nucleic acid bound to an inert support.

Accordingly, the instant specification, which must be read in view of the existing prior art, provides description to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed. Therefore, withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

B. 35 U.S.C. § 112, Second Paragraph

Claims 21-32 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner asserts that the claims are confusing with regard to the term "modified" and whether this modification refers to the addition of an ETM or some other modification. As pointed out in the specification at page 20, lines 15-24, the nucleotide is modified, preferably amino-modified, prior to ETM addition. Accordingly, the modification referred to in the claims describes nucleotide modifications that occur prior to ETM addition. As the relationship of the ETM and the modified nucleotide is clear, withdrawal of this rejection is respectfully requested.

C. 35 U.S.C. § 102(b)

Claims 21, 24, 25, 27, 30 and 31 stand rejected under 35 U.S.C. § 102(b) as anticipated by Hurley et al., J. Am. Chem. Soc. 120:2194-2195 (1998). As discussed above, written

description for the claimed invention is found in the instant application and therefore is also present in the priority document as this application is a continuation of the priority document. As the priority document has a filing date of December 10, 1993, Hurley et al. is not prior art and therefore cannot form the basis for a rejection of the instant claims under 35 U.S.C. § 102(b). Accordingly, Applicants respectfully request withdrawal of the 305 U.S.C. § 102(b) rejection.

D. 35 U.S.C. § 103(a)

Claims 22, 23, 26, 28, 29 and 32 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hurley et al., J. Am. Chem. Soc. 120:2194-2195 (1998) in view of Chee et al., U.S. Patent No 6,355,431. As discussed above, written description for the claimed invention is found in the instant application and therefore is also present in the priority document as this application is a continuation of the priority document. As the priority document has a filing date of December 10, 1993, neither Hurley et al. or Chee et al. are prior art to the instant application and therefore neither can form the basis for a rejection of the instant claims under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request withdrawal of the 305 U.S.C. § 103(a) rejection.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance and early notification to that effect is respectfully requested. Please direct any calls in connection with this application to the undersigned attorney at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY LLP

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By: Renee M. Kosslak
Renee M. Kosslak, Reg. No 47,717 for
Robin M. Silva, Reg. No. 38,304

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Four Embarcadero Center
Suite 3400
San Francisco, California 94111-4187
Telephone: (415) 781-1989
Fax No. (415) 398-3249